# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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Subject to PTA? YES/NO
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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 05.08.2002 |
| Applicant's or agent's file reference<br>M0656/7063WO | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US01/07464 | 08/03/2001 | 08/03/2000 |

Applicant
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

| Name and mailing address of the IPEA/ | Authorized officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Faux, K<br><br>Tel.+49 89 2399-8062 |

Form PCT/IPEA/416 (July 1992)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| M0656/7063WO | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US01/07464 | 08/03/2001 | 08/03/2000 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N15/60 | | |
| Applicant<br>MASSACHUSETTS INSTITUTE OF TECHNOLOGY | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 26/09/2001 | 05.08.2002 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Mundel, C<br>Telephone No. +49 89 2399 7314 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US01/07464

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

| | | | | | |
|---|---|---|---|---|---|
| 1-69 | as originally filed | | | | |

**Claims, No.:**

| | | | | | |
|---|---|---|---|---|---|
| 1-19,28-60 | as originally filed | | | | |
| 20-27 | as received on | 15/07/2002 | with letter of | 11/07/2002 | |

**Drawings, sheets:**

| | | | | | |
|---|---|---|---|---|---|
| 1/17-17/17 | as originally filed | | | | |

**Sequence listing part of the description, pages:**

1-3, filed with the letter of 11.04.01

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 28-60.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 28-60.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   **see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-27.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 6-8, 10, 15, 18-22 |
| | No: | Claims | 1-5, 9, 11-14, 16-17 and 23-27 |
| Inventive step (IS) | Yes: | Claims | 18-19 and 21-22 |
| | No: | Claims | 1-17, 20 and 23-27 |
| Industrial applicability (IA) | Yes: | Claims | 7, 17-19 and 23-27 |
| | No: | Claims | 4-6, 9, 11, 15 and 20-22 (completely) and 1-3, 8, 10, 12-14 and 16 (partially) (see Citations and explanations) |

2. Citations and explanations
   **see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

A unity objection was raised by the International Search Authority (ISA). Since the applicant didn't pay additional search fees, only invention 1 (claims 1-27) has been searched and, therefore, examined.

**Re Item IV**

**Lack of unity of invention**

According to **Rule 13 PCT** an application must relate only to one invention or to a group of inventions so linked as to form a **single inventive concept**, i.e. having at least one common technical feature defining a contribution over the known prior art.

The IPEA agrees with the ISA advices that the present application lacks unity and identifies the following groups of inventions in the international application :

1. Claims : 1-27

   Methods for preventing proliferation of a tumor or for preventing tumor cell metastasis, comprising exposing a tumor cell to heparinase III, either native or modified.

   Methods for preparing therapeutic agents, i.e. HLGAG fragments, for tumor treatment comprising isolating of a portion of a tumor, treating it with heparinase III to produce HLGAG fragments, and isolating HLGAG fragments, possibly further comprising determining the sequence of the HLGAG fragments.

   Methods for treating a subject having a tumor, comprising administering to the subject a therapeutic, synthetic or isolated HLGAG fragment, identified or produced when the tumor is contacted with heparinase III.

   Pharmaceutical compositions comprising a therapeutic HLGAG fragment for preventing metastasis of a tumor cell, e.g. with an anti-cancer compound.

2. Claims : 28-49

A substantially pure heparinase III comprising a polypeptide according to SEQ ID NO:2, or having conservative substitutions thereof within residues non-essential to enzymatic function wherein at least one His residue from the group His36, His105, His110, His139, His152, His225, His234, His241, His424, His469 and His539 has been substituted with an Ala, Ser, Tyr, Thr or Lys residue.

A substantially pure heparinase III having a modified product profile which is at least 10% different than the product profile of native heparinase III.

A substantially pure heparinase III that can cleave a heparan sulfate having a modified k-cat value which is at least 10% different than a k-cat value of native heparinase III.

A pharmaceutical preparation comprising heparinase III as said.

An immobilized substantially pure modified heparinase III comprising a modified heparinase III as said and a solid support.

A method of specifically cleaving a HLGAG comprising contacting a HLGAG with a modified heparinase III as said. e.g. wherein the heparinase III is administered to subject in need for inhibiting angiogenesis, or wherein the heparinase is administered to a tumor, or wherein the heparinase III is administered in a polymeric delivery device or in a vehicle for injection r in a vehicle for topical application (e.g. to the eye), or wherein the method is a method for sequencing HLGAG fragments.

3. Claims : 50-54

Methods for treating or preventing a subject having a cancer or at risk of developing a cancer, comprising administering a therapeutic HLGAG fragment, e.g. a composition of HLGAG fragments wherein at least 50%, 75% or 90% f the HLGAG fragments are di- or tri-sulfated disaccharides, or wherein the therapeutic HLGAG fragment is free of mono- or unsulfated disaccharides.

4. Claims : 55-60

A method for preparing LMWH comprising contacting an HLGAG sample with a modified heparinase III molecule to produce LMWH.

A composition comprising LMWH produced by contacting an HLGAG sample with a modified heparinase III. Methods of treating or preventing, e.g. of a disorder associated with coagulation, or of a tumor, or of psoriasis, or of neovascularization comprising administering to a subject a composition as said.

The prior art contains the following documents :
- WO9513830 disclosing and claiming the inhibitory effect of heparinase on angiogenesis, e.g. in a tumor.
- WO9201003 disclosing and claiming glycosaminoglycan derivatives and their use, e.g. in impeding the formation of tumor metastases.
- R. Godavarti et al. (1996) Biochem. Biophys. Res. Commun. 225 : 751-758 and WO9412618 disclosing heparinase III and its encoding gene from Flavobacterium heparinum
- EP0244236 and EP0394971 disclosing the preparation of a low-molecular weight heparin (LMWH) by chemical or enzymatic degradation of heparin or heparan sulfate, e.g. with the help of heparinase, and its use in inhibition of angiogenesis and the treatment of tumors.

In the light of these prior art documents, a first problem underlying this application can be defined as the need for further means and methods for preventing proliferation of a tumor or for preventing tumor cell metastasis. The solution as disclosed and claimed can be summarized as the provision of such means and methods comprising compositions containing heparinase III, or therapeutic heparin-like glycosaminoglycan (HLGAG) fragments obtained with the help of heparinase III and methods for the preparation and sequencing of these HLGAG fragments comprising the use of heparinase III, as well as the use of these compositions.

A second problem underlying the current application in view of the prior art can b summarized as the need for further heparinases. The solution as disclosed and claimed can be summarized as the need for further heparinases. The solution as disclosed and

claimed can be summarized as the provision of native or modified forms (mutants) of heparinase III, and the uses of these modified heparinases III.

A third problem underlying the current application in view of the prior art can be summarized as the need for further methods for the preparation of LMWH. The solution as disclosed and claimed can be summarized as the provision of a method for preparing LMWH comprising the use of a modified heparinase III, as well as the use of said LMWH in the preparation of pharmaceutical compositions and their use in treating or preventing disorders and diseases.

In view of the fact that methods for treating or preventing tumor proliferation or metatastasis, e.g. comprising administering heparinases, glycosaminoglycans or LMWH are known, and methods for their preparation are known, in view of the different problems underlying the different solutions as disclosed and claimed, and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as special technical feature common to these solutions, the IPEA agrees with the ISA advices that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently there is a lack of unity and the groups mentioned above represent independent inventions.

The attention of the applicant is drawn to the fact that claims 1-27 further lack unity for the following reasons :

1. Claims 1-17 refer to methods for preventing tumor cell proliferation or metastasis by treating said cells with heparinase III.

2. Claims 18-19 refer to a method for preparing therapeutic HLGAG fragments for the treatment of a tumor by treating a portion of a tumor with heparinase III.

3. Claims 20-22 refer to methods of treatment of a subject having a tumor by administering a therapeutic HLGAG fragment to said subject.

4. Claims 23-27 refer to compositions comprising a heparinase III and a targeting molecule or a therapeutic HLGAG fragment.

The use of heparinase III (optionally linked to a targeting molecule) for preventing cancer being well known from documents D1 and D4 (see points V-3.1 and V-4 of the present opinion) and HLGAG fragments produced by heparinase III being well-known from documents D2 and D3 and the targeting (see points V-3.1 and V-3.2 of the present opinion), the IPEA fails to see what could be considered as an inventive common concept linking the different groups mentioned above. Therefore, the present application lacks unity and the different groups mentioned above represent independent inventions.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The present application refers to methods for preventing proliferation of a tumor or for preventing tumor cell metastasis comprising exposing a tumor cell to an effective amount of (optionally modified) heparinase III, optionally in association with additional anti-cancer drugs. The application also refers to a method for preparing therapeutic agents (HLGAG fragments) for the treatment of a tumor and to compositions comprising heparinase III or therapeutic HLGAG fragments and a targeting molecule for targeting heparinase III to the tumor.

2. **Reference is made to the following documents :**

D1: WO 96 01648 A (IBEX TECHNOLOGIES R AND D INC ;ZIMMERMANN JOSEPH (US); VLODAVSKY I) 25 January 1996 (1996-01-25)

D2: WO 94 21689 A (CANCER RES CAMPAIGN TECH ;LYON MALCOLM (GB); GALLAGHER JOHN THOMAS) 29 September 1994 (1994-09-29)

D3: WO 93 19096 A (CANCER RES CAMPAIGN TECH) 30 September 1993 (1993-09-30)

D4: WO 95 13830 A (MASSACHUSETTS INST TECHNOLOGY ;CHILDRENS MEDICAL CENTER (US)) 26 May 1995 (1995-05-26)

3. The amendments filed with the letter of 11.06.02 are allowable under articles 19(2) and 34(2)(b) PCT.
The comments filed by the applicant with the letter of 11.07.02 have been taken

into account for drafting the present communication.

## 4. Lack of novelty; article 33(2) PCT.

4.1 The document D1 discloses, inter alia, the fact that selectively removing heparan sulphate from cell surfaces while leaving the extracellular matrix intact inhibits cell proliferation by down regulating the cell's response to growth factors and that this can be achieved by targeting heparin or heparan sulphate degrading activities to the cell surface. The glycosaminoglycan degrading enzymes comprise heparinase I, II and III. The targeting of said enzymes can be achieved by **genetically engineering a ligand binding functionality** into heparinase proteins or by physically controlling the localized enzyme concentration through the method of administration. (Abstract). Means of administration are disclosed on p.32 and include topically administration or injection.
Claim 8 discloses a method to diminish the response of a cell to growth factors by directing a glycosaminoglycan degrading enzyme to the surface of targeted cells. Claim 9 specifies that targeting is achieved by incorporating a cell specific ligand binding function and heparin or heparan sulfate degrading activity into a **fusion protein** having glycosaminoglycan degrading enzyme activity and claim 11 specifies that the ligand is specific to or present in higher concentration in **cancer cells** as compared with normal cells. Claims 17-28 refer to pharmaceutical compositions comprising a glycosaminoglycan degrading enzyme in combination with a pharmaceutically acceptable carrier and, optionally, means for targeting the enzyme to cells or tissues (claims 23- 25).

Even if D1 principally deals with the use of heparinases for stimulating cell proliferation, D1 also discloses and claims the use of heparinases to inhibit cell proliferation by targeting said heparinase to the cell surface. The IPEA considers that the choice of an appropriate cell specific ligand binding function and its incorporation into a fusion protein would have been easily achieved by the skilled person.

Moreover, even if the mechanism of action of the heparinase III was not

known from the authors of D1, the method disclosed in D1 is the same as the method disclosed in the present application, i.e. targeting a heparinase - which can be heparinase III - to a tumor cell. Since no further indications are given in the methods of the present application, the IPEA assumes that the mere presence of heparinase III at the surface of a tumor cell will be sufficient to prevent proliferation of the tumor cell or metastasis.
Moreover, the IPEA considers that the fusion protein disclosed in D1 can be considered as a modified heparinase III.

Therefore, the subject-matter of claims 1-5, 9, 11-14 and 16-17 can not be considered as novel in the sense of article 33(2) PCT.

Since D1 claims compositions comprising a heparinase or a fusion protein between a heparinase and a targeting molecule consisting of a hormone, an antibody or an integrin, the subject-matter of claims 23-26 can not be considered as novel in the sense of article 33(2) PCT.

4.2 The subject-matter of claims 6-8, 10, 15, 18-22 and 27 has never been disclosed in the documents cited in the International Search Report (ISR). Therefore, claims 6-8, 10, 15, 18-22 and 27 are considered as novel in the sense of article 33(2) PCT.

## 5. Lack of inventive step; article 33(3) PCT.

5.1 The IPEA considers that the skilled person, knowing from the document D1 that tumor growth or metastasis could be prevented by targeting a heparinase (including heparinase III) to the surface of a tumor cell, would have contemplated to administrate the heparinase in conjunction with other well-known anti-cancer compounds.
Therefore, claims 8 and 15 can not be considered as inventive (article 33(3) PCT).

The IPEA is also the opinion that the treatment of a tumor with heparinase in vitro can also not be considered as inventive. Therefore, claims 7 lacks inventive step in the sense of article 33(3) PCT.

The selection of specific tumor to be treated can also not be considered as inventive as long as this selection is not motivated by a technical purpose. For the moment, the IPEA fails to see such a technical purpose for the selection of the prostate tumor and melanoma. Therefore, claim 10 can not be considered as inventive (article 33(3) PCT).

The attention of the applicant is also drawn to the fact that the document D4 deals with the use of heparinases - including heparinase III - for inhibiting angiogenesis. An application of the methods disclosed in D4 is the treatment of solid tumors. Different ways of administration of heparinase are discussed, including direct injection in tumors (p. 38-39).
Even if the purpose for administering heparinase III in D4 (inhibiting angiogenesis which is necessary for solid tumor growth and metastasis) is not the same as in the present application, the administration of said heparinase to tumor cells for treating cancer has been suggested in D4. Therefore, the subject-matter of claims 1-17 can not be considered as inventive over the teaching of D4 (article 33(3) PCT).

5.2 The document D3 discloses oligosaccharides having growth factor binding affinity. These oligosaccharides can be prepared from glycosaminoglycans such as heparan sulphate and can be used either to activate and stimulate FGF activity or inhibit FGF activity. The use of said oligosaccharides for therapeutic purposes in medicine is also disclosed (Abstract). Some of the glycosaminoglycans were depolymerised using heparinitase (i.e. heparinase III) (p. 33-34, Depolymerisation of HS to selectively produce sulphated oligosaccharides). Further purifications steps are disclosed (p. 34-38). The use of the oligosaccharides for **antitumour treatment** is suggested (p. 40, lines 19-21). Claim 11 discloses an oligosaccharide product obtained by digestion of heparan sulphate by heparinitase, claim 25 discloses a method for obtaining such an oligosaccharide product using heparinitase, claims 33-35 refer to the therapeutical use of such an oligosaccharide product as an active FGF-activity inhibiting agent for controlling or reducing cell growth or proliferation, inter alia **for inhibiting cancer cell growth and metastasis** using an oligosaccharide product according to D3.

The IPEA considers that, knowing from D3 that oligosaccharides obtained by heparinase III digestion of heparan sulphate could be used for reducing cell growth, inter alia for inhibiting cancer cell growth and metastasis, would need no inventive activity to consider linking said fragments to well-known targeting molecules in order to target said compounds to a cancer cell.

Therefore, the subject-matter of claims 20 and 23-27 can not be considered as inventive in the sense of article 33(3) PCT.

5.3 The subject-matter of claims 18-19 and 21-22 has never been disclosed or suggested in the documents cited in the ISR. Therefore, claims 18-19 and 21-22 are considered as inventive in the sense of article 33(3) PCT.

## 6. Industrial applicability; article 33(4) PCT.

Claims 4-6, 9, 11, 15 and 20-22 refer to method of treatment of the human or animal body.
The methods of claims 1-3, 8, 10, 12-14 and 16 (partially) can be considered as method of treatment of the human or animal body as long as they are practised in vivo.
For the assessment of the present claims 4-6, 9, 11, 15 and 20-23 (completely) and claims 1-3, 8, 10, 12-14 and 16 (partially) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

## 7. Further remarks concerning the application.

7.1 The attention of the applicant is drawn to the fact that, in the light of the prior art, the composition of the HLGAGs at the surface of a cell can greatly vary from one cell type to another. Therefore, the IPEA considers that it is questionable if the HLGAG fragments resulting from heparinase III treatment

of every type of tumor cell will result in the generation of HLGAG fragments having a tumor- or metastasis-preventing activity according to the present application.

7.2 Claims 23-27 refer to compositions comprising, inter alia, HLGAG fragments. The IPEA is the opinion that said claims are not clear for the following reasons :

(i) All heparinase III-generated HLGAG fragments will not have an effect for preventing tumor growth or metastasis. The IPEA considers that, faced to all the possible HLGAG fragments which could be generated by heparinase III treatment of a caner cell, the skilled will not be able to determine those having a tumor growth or metastasis-preventing activity without undue burden of experimentation.

(ii) The attention of the applicant is drawn to the fact that the HLGAG fragments, being products, should be defined in terms of technical features of the product. The IPEA is the opinion that the definition of the HLGAG fragments in term of process steps would also not be considered as sufficiently clear since the method for producing HLGAG fragments in the present application will give very different HLGAG fragments, depending on the nature of the HLGAG at the surface of the cell and the conditions of the heparinase III treatment.

20. A method for treating a subject having a tumor, comprising, administering to the subject a therapeutic HLGAG fragment to treat the tumor.

21. The method of 20, wherein the therapeutic HLGAG fragment administered to the subject is a synthetic HLGAG fragment generated based on the sequence of the HLGAG fragment identified when the tumor is contacted with heparinase III.

22. The method of 20, wherein the therapeutic HLGAG fragment administered to the subject is an isolated HLGAG fragment produced when the tumor is contacted with heparinase III.

23. A composition, comprising:

heparinase III or a therapeutic HLGAG fragment in an effective amount for preventing metastasis of a tumor cell and a targeting molecule for targeting the heparinase III to the tumor, in a pharmaceutically acceptable carrier, wherein the heparinase III or therapeutic HLGAG fragment is linked to the targeting molecule.

24. The composition of claim 23, wherein the heparinase III is a modified heparinase III.

25. The composition of claim 23, wherein the heparinase III is a native heparinase III.

26. The composition of claim 23, wherein the targeting molecule is a compound which binds specifically to an antigen on the surface of a tumor cell.

27. A composition, comprising:

heparinase III or a therapeutic HLGAG fragment in an effective amount for preventing metastasis of a tumor cell and an anti-cancer compound in a pharmaceutically acceptable carrier.

28. A substantially pure heparinase III, comprising: